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Infection History Determines Susceptibility to Unrelated Diseases

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Epidemiological data suggest that previous infections can alter an individual's susceptibility to unrelated diseases. Nevertheless, the underlying mechanisms are not completely understood. Substantial research efforts have expanded the classical concept of immune memory to also include long-lasting changes in innate immunity and antigen-independent reactivation of adaptive immunity. Collectively, these processes provide possible explanations on how acute infections might induce long-term changes that also affect immunity to unrelated diseases. Here, lasting changes the immune compartment undergoes upon infection and how infection experience alters the responsiveness of immune cells towards universal signals are reviewed. This heightened state of alert enhances the ability of the immune system to combat even unrelated infections but may also increase susceptibility to autoimmunity. At the same time, infection-induced changes in the regulatory compartment may dampen subsequent immune responses and promote pathogen persistence. The concepts presented here outline how infection-induced changes in the immune system may affect human health.

1. Introduction

People react differently to immunological challenges, such as infections or cancer, and show large variance in their susceptibility to inflammatory diseases, such as allergies or autoimmunity. The responsiveness of the immune system is naturally to a large degree determined by genetic factors. However, a series of recent studies have revealed that genetic factors can only explain about 50–75% of the immune trait variance and the immune profile of an individual is thus to an astonishingly large degree determined by environmental factors.[1,2] There is robust epidemiologic evidence that the decreasing frequency of infections in developed countries correlates with a rising prevalence of allergies and other inflammatory disorders, as already put forward in the hygiene hypothesis almost 30 years ago.[3] The hypothesis has since been expanded and adapted to account also for the rise in autoimmunity in developed countries.[4] Indeed, reduced incidence of infections and lower microbiotic diversity in developed countries correlate with an increased prevalence of clinical conditions that are caused by inappropriate immune responses, such as allergy and autoimmunity—and possibly even cancer.[5] These data indicate that both pathogenic and nonpathogenic microorganisms play a fundamental role in educating the immune system.[6] While the specific mechanisms regulating how the immune response to one pathogen alters the response to a later infection with another pathogen or the susceptibility to autoimmunity, allergy, or cancer have been studied in some individual combinations, a global picture of how infection history affects disease susceptibility is still lacking.

Twin studies have been used to determine heritable versus nonheritable influences in immune responses elicited by vaccinations and the development of autoimmune diseases and found that both aspects strongly affect the immunological status of an individual.[7] The microbes (commensal and pathogenic) an individual encounters throughout his or her life are most likely a major determinant for the nonheritable factors. Indeed monozygous twin pairs, from which only one twin acquired cytomegalovirus (CMV) infection, show greatly enhanced variation for immune parameters after the infection.[1] Chronic infections, like CMV, and continuous interactions with commensal microbiota thus shape the immune system. Intriguingly, accumulating evidence suggests that transient challenges, such as acute infections and vaccinations, also have nonspecific effects on the ability of the immune system to react to other diseases.[8,9] Several adaptations of the immune system that could contribute to this altered reactivity have been reported, which include changes in the innate and adaptive arm of the immune system as well as alterations in its regulatory mechanisms. The following sections illustrate the long-term changes that pathogen encounters elicit in these different parts of the immune system (**Figure 1**), how the sum of these changes contributes to shaping the immune system over time and how this may affect susceptibility to unrelated diseases.

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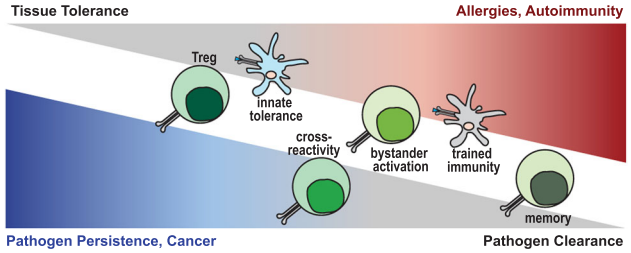


Figure 1. Overview of the impact of infection-induced adaptations of the immune system. Infections induce numerous specific and unspecific alterations in the composition and function of immune cells. These include induction of memory cells, cross-reactivity, bystander activation of T cells, and trained immunity of innate cells as well as changes in Treg abundance and composition. Each of these effects can, on the one hand, influence the ability of the immune system to fight and clear subsequent infections and may, on the other hand, promote tissue tolerance or inflammation.

2. Infection-induced Changes in the Immune System

2.1. Infections Generate Pathogen-Specific and Heterologous Immunity

The capability to memorize previous pathogenic encounters and thereby confer superior protection if the same pathogen is re-encountered represents a well-established core feature of the vertebrate adaptive immune system. Memory T cells can rapidly re-expand and are activated upon engagement of their cognate antigen with their T-cell receptor (TCR). Antibody production by memory B cells furthermore contributes to rapid and more robust responses upon re-encounter with a specific pathogen. Although these mechanisms constitute the basis for vaccinations, early observations have noted that certain vaccines such as Bacillus Calmette-Guérin (BCG), which protects against tuberculosis, can improve overall childhood survival.[10] These observations have hinted that the immune system cannot only learn to defend its host against re-encounter with the same pathogens but might also become superior in fighting other, unrelated pathogens under certain circumstances. To date, a number of mechanisms have been described that are believed to contribute to heterologous immunity (**Table 1**). These include cross-reactivity and bystander activation of T cells as well as trained immunity of innate immune cells. A general feature of innate and adaptive immune cells that have participated in an immune response is an altered epigenetic landscape.[28,29] These alterations could put them in a "poised state" and add an additional layer of responsiveness towards inflammatory cues, such as cytokines and the engagement of germline-encoded receptors, during heterologous immune challenges. To date, a number of studies have shown how mechanisms of heterologous immunity can, on the one hand, contribute to protection against newly encountered infections of their host but, on the other hand, pose a potential risk for immunopathology or the establishment of autoimmune disorders.

Table 1. Impact of infection-induced adaptations of the immune system on heterologous protection.

Process	Protection against heterologous infection	Reference
Memory	–	
Cross-reactivity	↑ or ↓	[42–44], [46] or [36], [45]
Bystander activation	↑	[57], [58]
Trained immunity	↑	[13–15]
Microbiota/chronic infection	↑ or ↓	[61–63] or [73]
Physical remodeling	↓	[9], [64]
Tregs	↓	[73–75]

2.2. How Selective Are Adaptive Immune Cells?

The most striking feature of T cells and antibodies produced by B cells is their unique specificity for their cognate antigen. This enables the formation of immunological memory, directed responses, and protects from the emergence of autoreactive T cells. But just how specific are T cells and antibodies really? About two decades ago, Mason[30] argued that cross-reactivity of the TCR is required for robust immunological protection. He supported this hypothesis with a simple but conclusive model, in which the number of monospecific naïve T cells required to cover all possible foreign peptides would be impossible to generate and maintain in a physiological context. Indeed, cross-reactivity has emerged as a common, or even necessary, feature of T cells and antibodies with potentially beneficial and adverse consequences for the host.[31]

Whether a T cell or an antibody cross-reacts with different antigens is determined by the sequence and structural similarities of these antigens. Such similarities, also known as molecular mimicry, can occur between self- and foreign antigens.[32] Importantly, molecular mimicry can result in autoimmunity through inappropriate responses of cross-reactive T cells that were primed during microbial encounters and are subsequently activated by recognition of self-antigens.[32,33] Conversely, T-cell clones with a strong affinity towards a specific self-antigen will be deleted during their maturation process and thereby the T-cell pool responsive towards a similar microbial or tumor antigen might be reduced.[34]

In addition to this, cross-reactivity towards different foreign antigens was also frequently observed in subsequent infections with related but also unrelated viruses. Some studies have shown that cross-reactive memory T-cell clones can be favored over non-cross-reactive clones during heterologous infections, thereby altering the relative contributions of different T-cell clonotypes, also known as immunodominance (**Figure 2**).[35] In extreme cases this could skew the immune response towards cross-reactive epitopes and thereby facilitate viral escape by mutation of the respective epitope.[36] Although cross-reactive memory T cells could help to confer protective immune

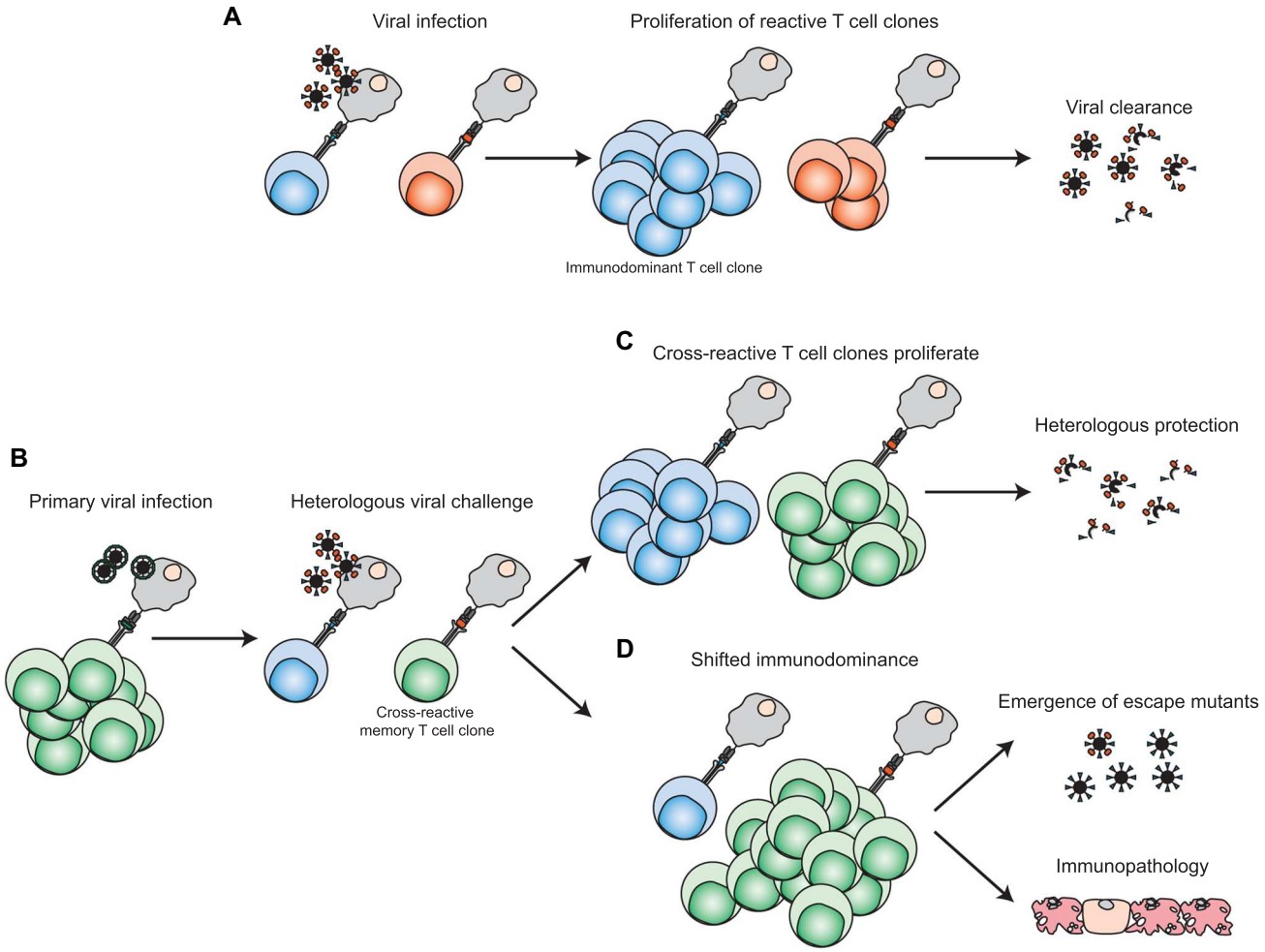


Figure 2. Cross-reactive T-cell clones can influence the outcome of heterologous infections. A) During an infection, T cells specific for pathogen antigens will proliferate and contribute to pathogen clearance. Different T-cell clones recognizing various antigen epitopes will respond, some showing more dominance than others. B) Memory T cells that differentiated during a previous acute infection may be cross-reactive for antigens of an unrelated pathogen. These cross-reactive memory T cells harbor the potential to expand and produce cytokines in response to a heterologous challenge. C) Activation of cross-reactive memory T cells could facilitate faster pathogen clearance during the secondary infection. D) If the immune response is strongly shifted towards the cross-reactive T-cell clone, this can lead to adverse effects. Extreme immunodominance of one epitope might facilitate the emergence of viral escape mutants or excessive immune responses could lead to immunopathology.

responses towards unrelated pathogens, they also pose a risk for immunopathology.[37,38] This is showcased by a study, in which lymphocytic choriomeningitis virus (LCMV)-immune mice were challenged with influenza A virus (IAV) infection and the degree of IAV-specific T cells cross-reacting with LCMV-peptides correlated with the degree of lung injury.[39]

Several studies have also found evidence for the significance of cross-reactive T cells in human infectious diseases. Epstein–Barr virus (EBV) is a common infection in humans and well known as the causative agent of infectious mononucleosis (IM). IM involves pronounced activation and proliferation of CD8+ T cells and can vary considerably in severity. T-cell clones recognizing IAV epitopes were identified among the T cells activated during IM.[40] Moreover, the frequency of IAV and EBV cross-reactive CD8+ T cells was reported to correlate with disease severity during IM.[41] Conversely, a more recent study suggested that some IAV-specific T-cell clones might be protective against infection with EBV.[42] These contrasting results highlight that the relationship between cross-reactive T cells and the outcome of heterologous infections may be very complex and not only depend on the respective pathogens but also on the specific cross-reactive antigens or T-cell clones.

Antibodies and T cells are also commonly cross-reactive to different species of flavivirus, including the Zika virus (ZIKV) and the dengue virus (DENV). CD8+ T cells from DENV-immune mice can contribute to immunity against experimental ZIKV infection.[43] In line with these reports, a stronger T-cell response and altered immunodominance pattern were also observed in DENV-pre-exposed patients upon ZIKV infection.[44] In contrast to the potentially protective role of cross-reactive CD8+ T cells, several publications have indicated that cross-reactive antibodies from DENV-exposed humans or mice

can enhance ZIKV infection.[45] Thus, it is exceedingly difficult to dissect and determine the overall contribution of previous DENV exposure to infection with ZIKV or disease pathogenesis. Nevertheless, a recent epidemiological study of local residents in Brazil found that previous exposure to DENV is associated with a lower risk of ZIKV infection.[46]

Overall, the evidence for protective functions of cross-reactive T cells or antibodies in humans is still rare. This does not seem surprising, as it would likely not result in any clinical symptoms. However, memory-phenotype CD4+ T cells with specificities for human immunodeficiency virus (HIV), CMV, and herpes simplex virus (HSV) have been found in the blood of donors who were never infected with these viruses.[16] The same study also showed that IAV-specific T cells that expanded in individuals following flu vaccination were able to recognize other microbial peptides, thus indicating that vaccinations could induce long-lived T cells that cross-react with peptides derived from unrelated pathogens.

2.3. Training Shapes Innate Immunity

The long-standing dogma that memory features can only be acquired by adaptive immune cells has been overthrown by a number of studies within the last decade. Innate immune cells such as natural killer cells (NK cells) and myeloid cells can also form a type of memory that has been termed "trained immunity."[47] For instance, NK cells that were preactivated had a higher cytokine response upon reactivation.[48] Furthermore, preactivated NK cells showed higher proliferative capacity than nonactivated controls and could thereby maintain enhanced function.[49] Importantly, it was demonstrated that preactivation of NK cells can enable them to respond more potently towards tumor cells.[50] In contrast to other innate cells, NK cells are also able to form antigen-dependent memory by expression of the germline-encoded receptor Ly49H, which specifically recognizes a mouse cytomegalovirus (MCMV)-encoded glycoprotein.[51] Through this mechanism, MCMV-specific NK cells can generate a pool of long-lived memory cells.

Myeloid cells are also able to acquire a "trained" phenotype, which enables them to respond more efficiently to inflammatory stimuli. Trained monocytes were able to confer protection from reinfection with the opportunistic fungal pathogen *Candida albicans* in mice lacking adaptive immune cells.[11] This study also showed that β-glucans, a component of the fungal cell wall, could train the monocytes and induced changes in their histone methylation. Indeed, epigenetic changes have been shown to be a hallmark of trained monocytes.[28] Training of monocytes could also contribute to a potential heterologous protection through BCG vaccinations, which has been frequently discussed.[12] In a study addressing this hypothesis, monocytes from BCG-vaccinated donors acquired epigenetic modifications and exhibited higher functional responsiveness to heterologous inflammatory stimuli when compared to monocytes that were collected before vaccination.[13] Furthermore, a BCG vaccination trial in humans showed that epigenetic remodulation of monocytes correlated with cross-protection against experimental yellow fever virus (YFV) challenge.[14]

Different functional states in immune cells are accompanied and supported by changes in cell metabolism.[17] In accordance with this observation, metabolic and epigenetic changes associated with trained immunity are closely interlinked. BCG-induced trained immunity in monocytes is dependent on alterations of cellular metabolism, most notably the induction of glycolysis.[18] More evidence for the connection between trained immunity and metabolism was provided by a recent study, which showed that the metabolite mevalonate can induce trained immunity in monocytes.[19] Because monocytes are rather short-lived cells, the question arose whether their precursor cells in the bone marrow might acquire a different phenotype through immune training and thereby influence myelopoiesis. A combination of three studies approaching the subject with different murine models of immune training—β-glucan administration, BCG vaccination, and sterile inflammation induced by a high-fat western diet—all found that the hematopoetic precursors of myeloid cells were modified and thereby constitute an important component of trained immunity.[20]

However, trained immune cells may also be detrimental to host fitness in certain settings and contribute to disease manifestation. Monocytes isolated from patients with symptomatic atherosclerosis showed epigenetic modifications and expression levels of glycolytic enzymes that could be attributed to trained immunity.[15] Innate immune cells in the brain can also acquire a trained state and thereby affect central nervous system inflammation. In mice, inflammation-mediated modulation of brain-resident macrophages (microglia) affected neuropathology in diseases like an experimental Alzheimer's model.[52] Interestingly, the authors of the latter study found pronounced, microglia-dependent differences in brain cytokine content depending on the administration of the inflammatory stimulus. Repeated injection resulted in a tolerant state, whereas a single administration was connected to a training effect and therefore a lower threshold for activation. This highlights the ability of the innate immune system to adapt to different kinds of stimuli and thereby provides important insights for the design of immunotherapies.

2.4. T Cells Show Unexpected Talents

As previously mentioned, T cells express a TCR that is unique for each clonotype and can recognize its cognate antigen in the context of MHC presentation. Two additional signals are required in order to direct the T cell to an appropriate response or differentiation: the engagement of costimulatory receptors and signals provided by cytokines. However, depending on the differentiation status of T cells, they can also be activated independent of TCR stimulation and therefore respond in a nonspecific manner during a heterologous immune challenge. This phenomenon has been termed "bystander" or "innate-like" activation of T cells. While TCR-dependent activation of T cells is rather well described, the understanding of T-cell activation by cytokines or germline-encoded receptors without recognition of cognate antigen is still quite limited.

The first observations that memory-phenotype CD8+ T cells can be activated by cytokines in the absence of TCR signaling were already made about 20 years ago. In particular, the proliferation of memory-phenotype CD8+ T cells in mice could be induced with cytokine interleukin-15 (IL-15).[53] Some groups that observed bystander activation or proliferation of T cells have argued that the biological relevance would be rather minimal.[54] Although this may be true for the models used in the respective studies, other groups have argued for a significant contribution of bystander T cells in various settings. It has become clear that innate-like activation of memory T cells depends on a number of variables like the cytokine environment, tissue homing or residency, and ligand expression of other cells, which are likely not met by all commonly examined virus infections or inflammation models. Importantly, the cytokine profile that is induced by innate cells during a heterologous challenge needs to fit the requirements for innate-like activation of T cells. Some cytokines, in particular IL-12, IL-18, or IL-15, were shown to potently induce interferon-γ (IFN-γ) production or cytolytic activity in memory CD8+ T cells.[55] In mouse models, activation of memory CD8+ T cells in an antigen-independent manner contributed to protection against heterologous infection with *Listeria monocytogenes*.[56] In addition to cytokines, engagement of germline-encoded receptors can also contribute to TCR-independent activation of memory CD8+ T cells. Such receptors can be expressed by innate as well as adaptive immune cells and detect a wide range of signals that are associated with infections or malignant cells. Some adaptive immune cells can also be activated in the absence of their cognate antigen through the recognition of these general signals in combination with cytokine stimuli. NK receptors like NKG2D are broadly expressed on memory CD8+ T cells in mice and humans. Antigen-independent activation of memory T cells through NKG2D engagement could have beneficial effects for early pathogen control and thereby support innate immunity.[57] In contrast to this protective role, engagement of NKG2D in bystander memory T cells may also result in immunopathology under certain conditions, as shown in the context of *Leishmania major* infection in mice.[58] In humans, NKG2D engagement on CD8+ T cells is thought to contribute to immunopathology in celiac disease.[25] Furthermore, a recent report described how TCR-independent activation of memory CD8+ T cells by IL-15 and NK-receptor engagement might significantly contribute to liver injury in patients during acute hepatitis A virus infection.[26]

Overall, these findings reveal that innate-like activation of bystander T cells might have a significant impact on disease outcome depending on the inflammatory context (**Figure 3**). It has become clear that cytokines released by innate cells and engagement of NK receptors can trigger TCR-independent activation of memory or effector T cells and thereby add an additional layer to the immune response. Nevertheless, many important questions concerning this mode of T-cell activation remain to be answered: for instance, which specific T-cell subsets can be activated independent of antigen recognition.

2.5. Microbe Exposure Shapes the Immune System

The human body is not just challenged by infections; it is also colonized by a diverse collection of viruses, as well as the microbiota, which is composed of microorganisms like bacteria, fungi, and protists. The microbiota mostly resides at barrier sites such as the skin or the gut and plays an important role in training and shaping the host immune system, allowing for induction of protective immunity to combat infections but also the establishment of immune tolerance.[59] However, changes in the microbiota composition or diversity induced by hygiene conditions,

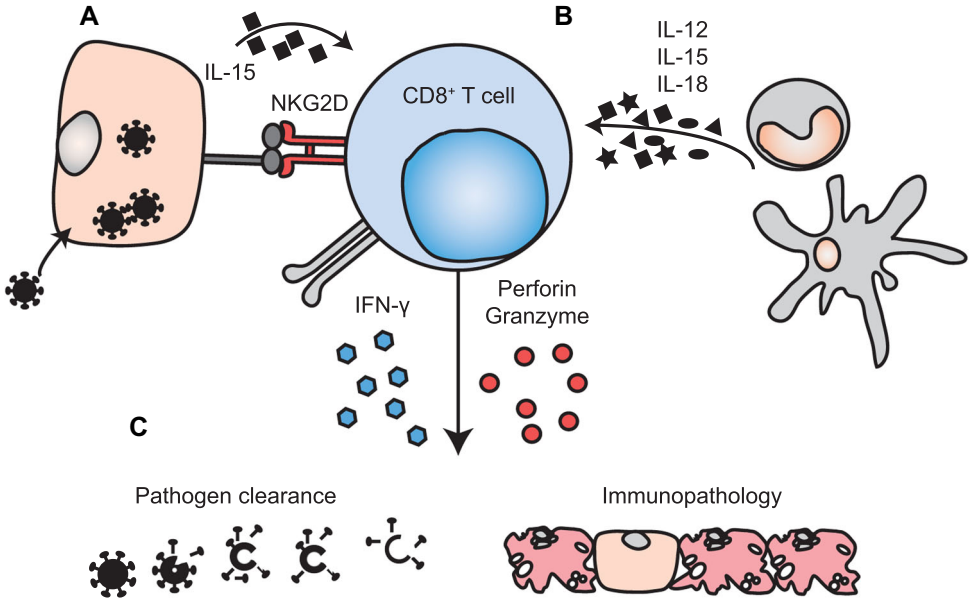


Figure 3. TCR-independent activation of T cells. A) NKG2D-expressing memory CD8+ T cells can be activated by IL-15 and expression of NKG2D ligands on transformed or infected cells. B) Some cytokines activate memory CD8+ T cells in the absence of TCR signaling. C) Both of these mechanisms can lead to the secretion of IFN-γ or cytotoxic molecules like perforin and granzymes. This can confer protection against heterologous pathogens but, under some circumstances, may also lead to tissue damage.

overuse of antibiotics, or diet can prevent the maturation and maintenance of a healthy and balanced immune system and predispose to inflammatory diseases and autoimmunity. Furthermore, depending on the context, commensal microorganisms can become pathogenic and vice versa.[60] Microbiota as well as ongoing chronic infections continuously condition cells of the immune system and thereby enable a rapid response to infectious challenges through trained immunity and bystander activation. This is illustrated by the observation that antibiotic treatment, which leads to a transient elimination of the bacterial microbiota, markedly reduces the efficacy of vaccinations as well as parasite-specific immune responses.[27] Similarly, several chronic infections were shown to enhance immune responses to unrelated pathogens.[61] At the same time, the heightened state of alert in persistent virus infections can also enhance immune responses that are harmful to the host as, e.g., those causing colitis or other inflammatory disorders and thus exacerbate disease.[62]

2.6. Infections Can Cause Long-Lasting Physical Changes

In addition to changing the composition and function of immune cells, infections often also induce physical changes in the host that, in some cases, even persist after the infection has been cleared. These changes can alter the microenvironment of the affected organ as outlined here for sepsis or they can induce persisting structural changes as seen in *Yersinia pseudotuberculosis* (*Y. pseudotuberculosis*) infection. These changes have a large impact on subsequent immune responses as they alter the ability of the host to counter infections but also influence the development of inflammatory disorders and therefore affect susceptibility to a broad spectrum of diseases that are not related to the initial infectious agent.

Severe, life-threatening infections can trigger massive immune responses that are known as sepsis. Severe sepsis entails multiorgan dysfunction and is often accompanied by sepsis-induced immunosuppression and a high risk of developing pneumonia. This immunosuppressed state persists for weeks even after patients appear to have "recovered" from sepsis itself.[63] A recent study revealed that the primary infection induces lasting changes in the local microenvironment in that it promotes the induction of regulatory T cells (Tregs). These dampen the immune response and compromise effective immune responses to a secondary challenge, leaving the host susceptible to infections.[64] This suggests that intervention strategies that interfere with Treg induction or function may be able to revert the generalized immune suppression in sepsis patients and improve their survival. Indeed, blockade of the PD-1/PD-L1 pathway, which interferes with Treg function, can restore immune function and improve survival of sepsis patients.[65] Overall, this suggests that preceding infections induce long-lasting changes in the local cytokine milieu, immune cell composition, and function that can alter the susceptibility to subsequent immune challenges.

The potent immune responses induced to rapidly eliminate the infectious agents are often also accompanied by a certain degree of collateral tissue damage. Once the infection is cleared, tissue damage is usually repaired and function is restored. However, in some instances, such as in *Y. pseudotuberculosis* infection, extensive structural changes occur and persist even after the infection is cleared.[9] Acute infection with *Y. pseudotuberculosis* results in the relocation of dendritic cells that persists even beyond the clearance of *Yersinia* and leads to a markedly reduced efficacy of subsequent oral vaccinations.[9] At the same time, the sustained inflammation might set the stage for chronic disorders, such as inflammatory bowel disease or celiac disease, which share many features with the inflammation induced by *Yersinia* infection.[66] Infection-induced structural changes can thus serve as a direct link between acute infections and the development of chronic inflammatory disorders.

In both examples listed here, sepsis and *Yersinia* challenge, the infection leads to long-lasting changes in the local cytokine milieu that can be immune suppressive or stimulating and persists beyond the clearance of the infection. Given their constant exposure to external challenges as well as constant stimulation through commensals, barrier tissues might be at particularly high risk of accumulating these kinds of immunological scars, predisposing for inflammatory disorders such as inflammatory bowel or celiac disease, psoriasis, allergies, or asthma but also infectious diseases such as pneumonia or gastrointestinal infections.

2.7. Pathogen Encounter Shapes the Regulatory Immune Response

Pathogen encounter not only initiates a proinflammatory immune response to eliminate the infection, but also induces a regulatory response that balances these effects to limit immunopathology resulting from excessive activity. At the same time, these regulatory responses can favor pathogen persistence and chronic infections. Myeloid suppressor cells, regulatory B cells, and Tregs are the mediators of this regulatory response. Tregs act through diverse mechanisms,[67] and like all T cells, are activated through the engagement of their TCR by antigen together with costimulatory signals.[68] However, in contrast to conventional T cells, the TCR repertoire of Tregs is shifted towards self-antigens.[69] This implies that Tregs can be activated independently of foreign antigen in all settings that enhance costimulatory signals. Once activated, their suppressive mechanisms allow Tregs to inhibit responder T cells irrespective of their antigen specificity, a mechanism known as bystander suppression. Furthermore, cytokines released upon tissue damage, such as IL-33 and IL-18, have been shown to be able to activate Tregs even in the absence of a TCR signal,[70] allowing Tregs to rapidly respond to tissue damage in a bystander fashion and limit immune pathology by dampening the immune response. Pathogen- or microbiota-induced changes in Treg frequency or function could therefore have a strong impact on immune responses to heterologous challenges.

The composition of the microbiota has been shown to be a major determinant for the induction of pro- versus anti-inflammatory T-cell responses. While segmented filamentous bacteria promote proinflammatory T-cell responses and systemic autoimmunity,[71] *Clostridia* and their metabolic by-products induce Tregs that have systemic suppressive effects and contribute to maintaining immune homeostasis.[72] Similarly, persistent pathogens often induce an increase in Tregs

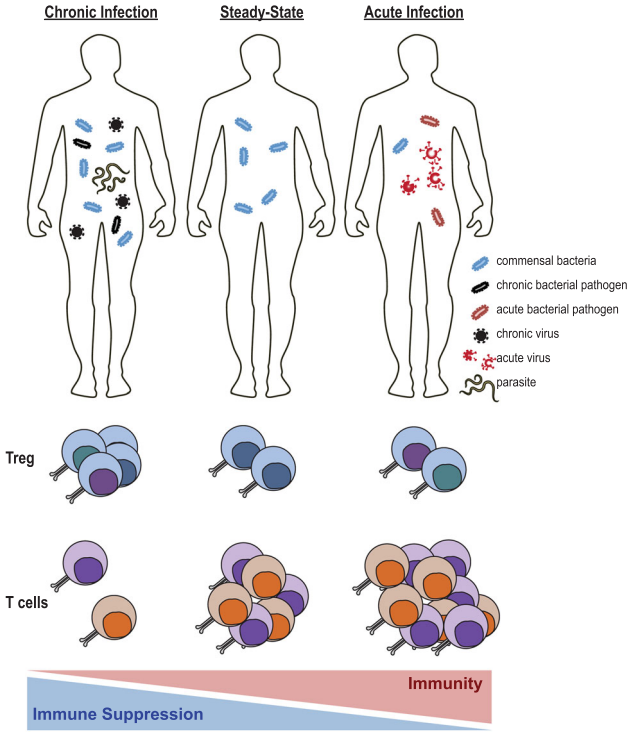


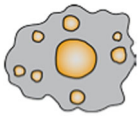
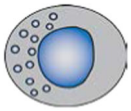
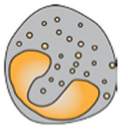
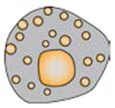
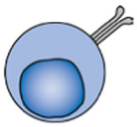
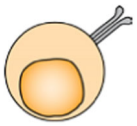
Figure 4. Impact of acute and chronic infections on immune cell composition and function. At steady state the body is colonized by commensals and a balanced immune composition is maintained (middle). Chronic infections by viruses, bacteria, or parasites lead to a dominance of regulatory T cells (Tregs) and as a consequence suppress the effector response and immunity (left). Acute infections induce the expansion of effector cells, which mediate pathogen clearance and immunity, as well as changes in the Treg composition (right). Overall, these changes in immune cell composition and function affect the long-term responsiveness of the immune system and its ability to react to immune challenges.

and thereby limit the pathogen-specific immune response, allowing for pathogen persistence (**Figure 4**). This extends to all classes of persistent pathogens, including chronic viral, bacterial, and parasitic infections, such as tuberculosis, leprosy, or malaria, where patients with poor anti-pathogen responses and persistent disease show an increase in Tregs.[73] An extensive body of work also outlines the central role of Tregs in parasite persistence in helminth infections and the extensive interplay between the parasites and the immune system.[74] Importantly, the generalized suppression of immunity by helminth-induced Tregs also extends to modulation of unrelated immune responses, as helminth-infected patients show reduced immune responses towards childhood vaccines or other parasites.[75] Given that coinfections with helminths and malaria and/or tuberculosis are still frequent in many low-income countries, it will be important to determine whether the immune-suppressive effect of pathogen-induced Tregs continues to increase with increasing infectious burden and how this could be counteracted to allow for pathogen clearance and efficient vaccination strategies against prevalent diseases.

Interestingly, the high levels of parasitic infections in low-income countries also seem to have beneficial effects in that inflammatory and autoimmune disorders are much less frequent than in the developed world.[74] In a cohort of Argentinian multiple sclerosis patients, individuals who unintentionally acquired a helminth infection displayed elevated Treg frequencies and remission from the symptomatic disease. This was reversed upon anti-helminth treatment and accompanied by a loss of the regulatory response and clinical relapse.[21] These findings could also be recapitulated in experimental animal models where helminth infection protects mice from inflammatory disorders such as celiac disease and allergy and this protection can be transferred to naïve animals via Treg transfer.[22] These findings have led to therapeutic approaches in clinical trials that capitalize on the ability of parasite extracts to induce Tregs and thereby dampen inflammatory immune responses. The stimulation of Treg activity has thus emerged as a central concept that explains the beneficial effects of certain microbiota and parasitic infections in ameliorating inflammatory diseases such as allergy and autoimmune disorders as well as improving transplantation tolerance.[23]

Recent research has also revealed that Tregs themselves represent a mixture of functionally diverse subsets. Furthermore, infectious challenges can transiently alter the composition and function of Tregs to allow for the induction of anti-pathogen responses but also efficiently shutting down the effector response once the infection has been cleared (Figure 4).[24] Most likely, these temporary changes in Treg composition not only affect immune responses against the ongoing infection but also would alter suppression of autoreactive immune cells or cells specific for persistent pathogens. Indeed, epidemiological data revealed that several autoimmune diseases show a correlation with certain pathogens, although these do not induce the disease. In the case of multiple sclerosis, many different viruses were investigated as a possible cause, most recently EBV. However, there is no proof

Table 2. Potential impact of primary acute infections on immune cell activation during heterologous immune responses.

Branch	Cell type		Mechanisms	Possible disease associations	Potential impact on host
Innate	Macrophages		• Epigenetic changes in progenitor cells	• Heterologous protection[13], [14]	Beneficial
			• Proinflammatory phenotype	• Neuropathology[52]	Harmful
			• Enhanced responsiveness	• Atherosclerosis[15]	
	NK cells		• Cytokine-induced epigenetic changes	• Antitumor responses[50]	Beneficial
			• Cytokine production	• Heterologous protection?	
			• Cytotoxicity	• Tissue damage? (mechanism may be similar to memory bystander CD8+ T cells)	Harmful
	Granulocytes		• Epigenetic changes in progenitor cells?	• Heterologous protection?	Beneficial
				• Allergic disease?	Harmful
	Mast cells		• Epigenetic changes?	• Heterologous protection?	Beneficial
				• Allergic disease?	Harmful
Adaptive	Effector and memory CD8+ T cells		• Epigenetic changes	• Heterologous protection[56], [57]	Beneficial
			• Cytokine production	• Antitumor responses?	
			• Cytotoxicity	• Tissue damage[25], [26], [58]	Harmful
	Effector and memory CD4+ T-helper cells		• Epigenetic changes	• Heterologous protection?	Beneficial
			• Cytokine production	• Autoimmunity?	Harmful
	Regulatory T cells		• Epigenetic changes?	• Tissue protection?	Beneficial
			• Tissue abundance?	• Immune homeostasis?	
			• Enhanced responsiveness?	• Promoting pathogen persistence?	Harmful
				• Hampered antitumor responses?	

that any of them causes multiple sclerosis.[76] Similarly, there is a strong correlation between enterovirus species and type 1 diabetes, but again, there is no indication that the virus can actually cause islet destruction.[77] As such, the viral infections that are associated with the diseases likely serve as their environmental triggers without being the causative agent. We propose that in addition to infection-induced training of innate immunity, bystander activation of memory cells and reactivation of cross-reactive lymphocytes, changes in Treg composition and function may allow an autoreactive immune response to unfold and thus contribute to the manifestation of autoimmune diseases. In contrast, infection-induced changes in Treg composition could also result in a more potent suppression of immune responses and thereby promote pathogen or tumor persistence.

2.8. Speaking the Same Language—Educated Immune Cells Respond to Universal Signals

As outlined in the preceding sections, infections trigger long-lasting changes in both the innate and adaptive arm of the immune system that go far beyond classical memory. Infection experience seems to equip both types of immune cells with an altered responsiveness towards two types of universal signals: cytokines and the ligation of germline-encoded receptors. Innate cells are thus able to respond more quickly and potently as observed in trained immunity. Adaptive immune cells are able to rapidly participate in an immune response even in the absence of their cognate antigen as observed in bystander activation. Following infection, immune cells adopt a state of alertness that persists even beyond pathogen clearance and is maintained by epigenetic modifications.[28,29] This education of the immune system likely re-enforces a first line of defense in heterologous challenges and thereby reduces the magnitude of the immune response required to control the secondary infection and allows the host to preserve its resources. In addition, this heightened responsiveness might serve as a means to compensate for the loss of clonal diversity that is observed with age and contributes to the higher susceptibility of older people to infections.[78] Indeed, a recent study found that the effect of non-heritable factors on the immune response becomes more dominant with age, most likely due to the accumulating effect of environmental influences.[1,79] Interestingly, the frequency of Tregs was more strongly

determined by environmental factors with progressing age,[1] suggesting that infection-induced changes in Treg frequencies and function might be an important factor in shaping the immune response and determining susceptibility to infectious and inflammatory diseases.

Trained immunity and bystander activation both show positive effects on pathogen control and maybe even anti-cancer immunity as outlined above (**Table 2**).[50] At the same time, heterologous immunity can also have negative consequences for the host such as increased tissue damage as seen in hepatitis[26] and likely also contributes to disease in the context of autoimmunity. Most of the changes observed in an experienced immune system reported to date result in enhanced inflammatory responses and increased cytotoxicity (through NK and cytotoxic T cells). Whether similar mechanisms also exist in cells contributing to allergic responses or anti-helminth immunity, such as mast cells, eosinophils, or T helper cells, remains to be determined (see Table 2). Similarly, how cells participating in a heterologous response are regulated is still completely unclear. While Tregs have been shown to have tissue protective effects upon antigen-independent activation,[70] it is unclear which cell type might dampen and limit heterologous immunity to prevent immune pathology. Although many questions still remain open, recent developments have made it clear that immune cells are more versatile than previously appreciated. In addition to their classical functions, infection-experienced immune cells rapidly respond to stimulation by cytokines or germline-encoded receptors and initiate potent heterologous immune responses that contribute to pathogen control but might also enhance immune pathology.

3. Conclusions and Outlook

The concepts presented here outline how pathogens and commensals induce long-term changes in the immune system that affect subsequent immune responses and impact human health. Animal models and clinical studies show that vaccinations, prior infections, or coinfections can modify the immune response to unrelated pathogens. Additionally, a number of inflammatory diseases have been linked to infections but finding direct associations between pathogens and the initiation of these disorders has remained difficult. This might in part be due to the fact that infections can induce long-term changes in the immune system that may persist even once the infection is cleared. These effects likely accumulate over time and the onset of inflammatory disease does not have to coincide with the infectious trigger (s). Similarly, infection history can also induce changes that enhance the regulatory properties of the immune system and thus favor the establishment of chronic infections and prevent protective immunity against cancer. Future work should be aimed at further unraveling the mechanistic basis for these changes in the immune system and most importantly also at bringing these concepts together to reveal a more comprehensive picture of the mechanisms underlying heterologous immunity.

Each new infection or immune trigger an individual is exposed to during a lifetime will educate and potentially alter the dynamics of their immune system and it is important that this is taken into account in preclinical models. Future research should identify the factors that shape the immune system in these processes and determine how heterologous secondary immunity affects vaccine efficiency and immune therapies targeting inflammatory disorders or cancer to be able to optimize preventive and therapeutic interventions in the future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

bystander activation, disease susceptibility, heterologous immunity, infections, trained immunity

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